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PRIMARY PLERIXAFOR MOBILIZATION IN AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANT CANDIDATES AT HIGH RISK FOR MOBILIZATION FAILURE

Shapiro, J., Bookout, R., Perkins, J., Ayala, E., Alsina, M., Field, T., Kharfan-Dadaja, M.A., Perez, L.E., Ochoa-Bayona, J.L., Tomblyn, M., LaFave, D., Anasetti, C., Fernandez, H.F. Moffitt Cancer Center, Tampa, FL

Plerixafor has recently become commercially available for use as a mobilizing agent in patients undergoing CD34+ hematopoietic cell collection in preparation for autologous transplantation. Practice guidelines were developed to optimize the use of plerixafor at our institution. Within those guidelines, we defined patients at high risk for mobilization failure as those who met the following criteria: 1) Received 3 lines of prior chemotherapy; 2) Received 2 lines of prior chemotherapy plus a radioimmunoconjugate 3) Received 2 lines of prior chemotherapy plus radiation therapy to extensive fields; 4) Received 4 or more cycles of hyper-CVAD or more than 4 cycles of lenalidomide; 5) Hypocellular marrow (<25% cellularity); 6) Platelet count <100,000/μL

We report here preliminary data on 19 consecutive high-risk patients who have received plerixafor as primary mobilization therapy. The median age of the patients was 60 (range 33-71) years. Diagnoses include multiple myeloma (12), non-Hodgkin's lymphoma (6) and Hodgkin's disease (1). Patients received a median of 2 (range 1-5) lines of prior chemotherapy and 6 patients also received prior radiation therapy. All patients received 4 doses of G-CSF (10 mcg/kg/d) and on the evening of the forth dose, they also received plerixafor 0.24 mg/kg except for 3 patients who were dosed at 0.16 mg/kg due to reduced creatinine clearance. Apheresis was started the morning after the first dose of plerixafor. G-CSF, plerixafor, and apheresis were continued until at least 2×10^6 CD34+ cells/kg were collected. The median number (range) of G-CSF doses, plerixafor doses and aphereses were 4 (4-7), 1 (1-3), and 1 (1-3), respectively. The number of patients collecting at least 2×10^6 CD34+ cells (cumulative) on 1, 2, and 3 aphereses were 15 (79%), 17 (89%), and 19 (100%). The median (range) of the total number of CD34+ cells/kg collected for all patients was 4.99 (2.07-23.65)x 10^6. All patients have been transplanted. Eighteen patients are evaluable for neutrophil recovery; median time to absolute neutrophil count > 500/μL was 12 (range 10-12) days. Fourteen patients have recovered platelet counts > 20,000/μL (without transfusion for 7 days) at median of 18 days (range 14-42) post-transplant. We conclude that plerixafor is beneficial in patients who are at high risk for mobilization failure with 100% of patients mobilizing adequate CD34+ cells counts in 3 aphereses or less.

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AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION WITH INDUCTION OF AUTOLOGOUS GRAFT-VERSUS-HOST DISEASE IN ACUTE MYELOID LEUKEMIA – LONG-TERM F/U DATA

Park, J.[1], Park, S.H.[2], Kim, S.Y.[3], Ko, Y.[4], Kim, K.[2], Jung, C.W.[2], Lee, J.H.[1], Lee, H.M.[3] [1] Gachon University of Medicine and Science, Gil Medical Center, Incheon, Korea; [2] Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [3] Konkuk University Hospital, Konkuk University School of Medicine, Seoul, Korea; [4] Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

We previously published data that suggested that induction of an autologous graft-versus-host disease (GVHD) has an anti-leukemic effect, consequently increasing the survival rate of patients who undergo autologous peripheral blood stem cell transplantation (PBSCT). Here we report the long term follow up data regarding the overall survival (OS) and disease free survival (DFS). In total, 22 acute myeloid leukemia patients with favorable and intermediate cytogenetic risk, in their first complete remission, were administered cyclosporine c.i.v. from day 0 to day +28 at a dose of 3.0 mg/kg per day and interferon- γ (IFN- γ) at 0.025 mg//m^2 s.c. every other day from day +14 to day +42 following autologous PBSCT. Natural-killer (NK) – cell activity assays and skin biopsies were performed. Engraftment was successful in all patients at a median of 13 days without any significant additional toxicity. Histologically confirmed that cutaneous GVHD had developed in 12 patients, and NK-cell activity was significantly augmented after the autologous PBSCT in those patients (P = 0.03). After a median follow-up duration of 117.6 months (range, 87.3-152.8), the 3-year DFS and OS rates were 68.2% and 72.7%, respectively, and the 5-year DFS and OS rates were 63.6% and 73%, respectively. They were without significant correlation with GVHD status or augmentation of NK-cell activity. The median OS was unreached yet.

This data suggests that the administration of cyclosporine and IFN-γ following autologous PBSCT improves OS and DFS, which may be attributable to the antileukemic effect, although no difference in survival rates could be demonstrated between cutaneous GVHD-positive and -negative groups.

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VALIDATION OF A DECISION-MAKING ALGORITHM TO GUIDE THE USE OF PLERIXAFOR FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL MOBILIZATION

Costa, L.J., Alexander, E., Hogan, K.R., Fouts, T.V., Kramer, C., Schaub, C., Stuart, R.K. Medical University of South Carolina, Charleston, SC

Background: Plerixafor, an inhibitor of CXCR-4/SDF-1 binding, is approved for mobilization of peripheral blood hematopoietic stem cells (PBHSC) prior to autologous hematopoietic stem cells transplantation (AHSCT) for non-Hodgkin lymphomas and multiple myeloma (MM). We developed a cost-saving decision making algorithm that utilizes the CD34+ count in the peripheral blood on the 4^{th} day of G-CSF administration (PB-CD34+) and the target CD34+ count for the specific patient (T-CD34+) to decide between starting collection on day 4 and continuing G-CSF administration only (G approach) or adding Plerixafor the night before each apheresis session and starting apheresis on day 5 (G + P approach). The algorithm was based on actual mobilization data and analysis of mobilization charges aiming at finding the approach likely to have the lowest charge for each circumstance. The development of this algorithm has been previously presented (ASH 2009, abstract 3216)

Methods: We reviewed mobilization and collection data on 28 patients who have completed mobilization on the MUSC mobilization algorithm. Additionally, we reviewed engraftment data for the 19 patients who have undergone a first autologous transplantation.

Results: Twenty eight patients have been included in the validation cohort. Patient characteristics are displayed in table 1. Nine patients (33%) completed collections with the G approach and 19 (68%) with the G + P approach. There were no collection failures. Twenty-six

Table 1. Characteristics of the patients included in the validation cohort

Characteristic	Number of patients	Percentage
Diagnosis		
Multiple Myeloma	23	82
Lymphoma	5	18
Age		
≤60	17	61
>60	11	39
Gender		
Male	10	36
Female	18	64
Prior radiation	10	36
Prior lines of therapy- Lymphomas		
≤2	5	100
>2	0	0
Prior lines of therapy- Myeloma		
≤1	10	43
>1	13	57
Prior lenalidomide	14	61
Target CD34+/kg for mobilization		
3x10e6	13	46
6x10e6	15	54

patients (93%) completed collection within the predicted number of apheresis sessions (78% for G and 100% for G + P, P = 0.03). Nineteen (68%) of the patients included in the validation cohort have received a first autologous transplant. Median cell dose was 3.81 $\times$ 10^6 (range 3.04-4.42 x10^6) CD34+/kg for the 8 patients in the G approach and 4.99 $\times$ 10^6 (range 3.00-7.49 x10^6) CD34+/kg for the 11 patients in the G + P approach. There was no difference between approaches in time for absolute neutrophil count > 500/mm^2 (median 12 days vs. 13 days for G and G + P respectively, P = 0.07) or platelet count > 20,000/mm^2 without platelet transfusion (median 11.5 days vs. 13 days for G and G + P respectively, P = 0.09)

Conclusion: The MUSC mobilization algorithm is a data-generated and accurate tool to decide on the utilization of plerixafor for mobilization, starting on the 4th day of G-CSF. This approach is likely to save on mobilization costs compared to the "on label" use of plerixafor in all MM and NHL mobilizations.

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READMISSION RATES AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Mohan, S., Overman, R., Dean, R., Smith, S., Kalaycio, M., Pohlman, B., Sweetenham, J., Sobecks, R., Andresen, S., Copelan, E., Bolwell, B. Cleveland Clinic Taussig Cancer Institute, OH

With increasing scrutiny of healthcare expenditures, policy proposals have highlighted the reduction in hospital readmission rates as a method by which to improve the cost and the quality of medical care. To date, readmission rates following bone marrow transplantation procedures have been sparsely described. A retrospective review of consecutive patients who underwent autologous hematopoietic stem cell transplantation (AHSCT) at a single institution over a five-year period was performed to determine the number and causes of readmission within one year post-transplantation. Each readmission was classified according to the primary presenting symptom or an identified etiology following inpatient clinical evaluation. 485 patients received high-dose chemotherapy followed by an AHSCT from 1/2004 to 12/2008 for varied disease indications including non-Hodgkin lymphoma (n = 252, 52%), multiple myeloma and/or amyloidosis (124, 26%), Hodgkin lymphoma (83, 17%), and other malignant diseases (26, 5%). Of these, 142 (29%) required at least one inpatient readmission within one year, accounting for 216 discrete events. 45 patients (9%) were readmitted more than once. 60 of all readmissions (28%) occurred within the first 30 days of transplantation, and 131 (61%) within the first 100 days. 45% of all readmissions were due to infection or unexplained fever, 17% to gastrointestinal causes, 13% to relapsed disease or new secondary malignancy, 8% to cardiopulmonary symptoms, and 6% to neurological symptoms, with the remainder of admissions related to thromboembolic disease, refractory pain symptoms, hepatic dysfunction, or other causes. Among those patients admitted within 30 days, 63% presented with infection or fever and 23% with gastrointestinal symptoms. The majority of those readmitted with gastrointestinal toxicity (9/14) were patients with non-Hodgkin lymphoma. Further study of this high-risk patient group and of the reasons for readmission may identify outpatient supportive care measures that could be enacted to decrease both AHSCT-related morbidity and associated healthcare costs.

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PLERIXAFOR GIVEN "JUST IN TIME" FOR PERIPHERAL BLOOD STEM CELL MOBILIZATION OF PATIENTS WITH SUBOPTIMAL RESPONSE TO G-CSF

Horwitz, M., Khan, T., Long, G., Gasparetto, C., Sullivan, K., Chute, J., Rizzieri, D., Drago, S., Chao, N. Duke University Health System, Durham, NC

Plerixafor reversibly inhibits binding of stromal cell-derived factor 1 alpha to the chemokine receptor CXCR4 resulting in mobilization of bone marrow hematopoietic progenitor cells. Phase III studies demonstrate that plerixafor given on day 4 of G-CSF treatment significantly improves the chances of successful peripheral blood stem cell collection compared to G-CSF alone in patients with multiple myeloma (MM) and non-Hodgkin lymphoma (NHL). In the context of an IRB approved phase II clinical trial, we studied whether plerixafor could be used to rescue patients who demonstrate a suboptimal mobilization response to five doses of G-CSF(10μg/kg). Patients were eligible for protocol therapy if, on day 5 of G-CSF, there was less than 7 circulating CD34+ cells/μl. In addition, patients with 7 to 20 circulating CD34+ cells/μl were eligible for protocol therapy if <1.3 $\times$ 10^6 CD34+ cells/kg were collected on the first day of apheresis. These patients were felt to be at high-risk for inadequate stem cell collection. Subjects were given plerixafor (0.24 mg/kg) at 10:00PM of day 5 of G-CSF therapy. This process of an evening dosing with plerixafor followed the next morning by G-CSF and apheresis was repeated for up to a total of 3 days of apheresis or until ≥5 $\times$ 10^6 cells/kg were collected. The primary endpoint of the study is the percentage of patients who collected at least 2 $\times$ 10^6 CD34+ cells/kg. Nine subjects (median age 59) have been accrued to the trial (MM 3, NHL 5, Hodgkin Lymphoma 1), with the results demonstrated in the table. Five of nine subjects had less than 7 circulating CD34+ cells/kg on Day 5 of G-CSF mobilization. The circulating CD34+ cell level increased a mean of 2.8 fold after the first dose of plerixafor and a mean of 1.8 fold after the second dose of plerixafor. All nine subjects achieved the primary endpoint of the study (collection of >2 $\times$ 10^6 CD34+ cells/kg). Plerixafor was well tolerated with no adverse events >grade 1. In conclusion, plerixafor can be given "just in time" to rescue patients with a poor mobilization response to G-CSF alone. Further studies are needed to assess the most cost effective way of using this potent stem cell mobilizing agent.

Mobilization Response to Plerixafor given "Just in Time"

PATIENT	DAY 5G-CSF (CIRCULATING CD34 + CELLS/μL)	DAY 6G-CSF + PLERIXAFOR DOSE 1 (CIRCULATING CD34 + CELLS/μL)	DAY 7G-CSF + PLERIXAFOR DOSE 2 (CIRCULATING CD34 + CELLS/μL)	DAY 8G-CSF + PLERIXAFOR DOSE 3 (CIRCULATING CD34 + CELLS/μL)	TOTAL CD34 + CELL YIELD (X 10^6)
1	5.4	20	3.3		2.2
2	6.7	30	19.7		3.6
3	16.3	16.3	5.1		2
4	13.2	15.6			2.9
5	4.6	19	4.7	5.9	2
6	5.7	7.4	7.4		2.2
7	5.8	17.8	13.4	10.3	5.9
8	11.2	26.8	22.3		3.4
9	7.3	26.6	22.3		3.6

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RITUXIMAB AND SARGRAMOSTIM IMMUNOTHERAPY FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANT FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA

Scigliano, E., Grosskreutz, C.L., Osman, K., Malone, A., Nieto, J., Isola, L.M. Mount Sinai Medical Center, New York, NY

Introduction: High dose chemotherapy with autologous stem cell transplant (ASCT) improves survival in patients with aggressive non-Hodgkin's lymphoma (NHL), but relapse occurs in 40-50% of patients. Rituximab exerts its anti-tumor effect through complement and antibody-dependent cell cytotoxicity (ADCC). Sargramostim is involved in the activation and differentiation of macrophages and dendritic cells and increases monocyte-mediated ADCC. The addition of sargramostim to rituximab may potentiate the anti-tumor effect of rituximab by enhancing recruitment and activation of effector cells that mediate ADCC. We evaluated the safety and efficacy of rituximab and sargramostim given as "adjuvant immunotherapy" to patients following ASCT for aggressive NHL.

Patients and Methods: 8 patients (5 male, 3 female; median age 53, range 34-69) with CD20+ diffuse large B cell (6) or mantle cell (2) NHL relapsed, primary refractory or in first complete remission (intermediate-high or high risk IPI) underwent stem cell mobilization using rituximab and cyclophosphamide followed by high dose